Therapeutic Implications of Peptide Transport Across the Blood-Brain Barrier

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Peptides can cross the blood-brain barrier (BBB) by both saturable and non-saturable mechanisms in quantities sufficient to explain some of their effects on the CNS after their peripheral administration. Some effects have been shown to require the peptide to cross the BBB. For example, changes in the EEG after the peripheral administration of the enkephalin analog Tyr-D-Ala-Gly-Met-Phe-Met(O)-ol can be blocked by the antiopiate naltrexone, which crosses the BBB, but not by the antiopiate methylnaltrexone, which does not cross the BBB. This shows that this effect is exerted through opiate receptors behind the BBB. The amount of peptide that accumulates in the brain depends on factors in addition to that of BBB permeability such as circulating half-time, volume of distribution, and binding in blood. Manipulation of these factors can help in targeting peptides to desired sites of action. For example, RC-160, a lipophilic analog of somatostatin with anti-tumor activity, crosses the BBB poorly partly because of binding in serum. Entry into brain tumors of RC-160, however, is nearly a magnitude greater than in normal brain because the blood-brain tumor barrier is less restrictive. The pharmacokinetics of cyclo His-Pro (cHP) also favor its therapeutic use. cHP is a small, lipophilic, cyclized, endogenous peptide that can reverse ethanol narcosis after direct injection into the brain. Its entry rate into the brain is very low, about $1/10^{th}$ the rate typical of peptides. However, it is very resistant to enzymatic degradation and has a long half-life in the circulation. As a result, cHP given iv is also capable of reversing ethanol narcosis at a dose about 200 times that required centrally. cHP is so stable that 25-50% of an oral dose enters the circulation. Oral cHP can also reverse ethanol narcosis at a dose about twice that given iv. This illustrates how even an endogenous peptide can possess the ability to be absorbed orally, circulate in the blood, cross the BBB, accumulate in the brain, and exert a therapeutically important action on the brain.